IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

DECLARATION OF BERTRAM A. SPILKER, M.D., Ph.D., F.C.P., F.F.P.M., IN SUPPORT OF DEFENDANT'S MARKMAN BRIEF

Richard K. Herrmann (I.D. No. 405)
Mary B. Matterer (I.D. No. 2696)
MORRIS JAMES LLP
500 Delaware Avenue, 15th Floor
Wilmington, DE 19801
Telephone: (302) 888-6800
mmatterer@morrisjames.com

Daralyn J. Durie
Asim Bhansali
Paula L. Blizzard
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 94111
Telephone: (415) 391-5400

M. Patricia Thayer
John M. Benassi
Jessica R. Wolff
Daniel N. Kassabian
Samuel F. Ernst
HELLER EHRMAN LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92101
Telephone: (858) 450-8400

Attorneys for IMPAX LABORATORIES, INC.

Original Dated: May 8, 2007
Public Version: May 15, 2007

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **FILED UNDER SEAL**

DECLARATION OF BERTRAM A. SPILKER, M.D., Ph.D., F.C.P., F.F.P.M., IN SUPPORT OF DEFENDANT'S MARKMAN BRIEF

I, Bertram A. Spilker, M.D., Ph.D., F.C.P., F.F.P.M., declare:

1. I am a physician, pharmacologist, clinical trials and drug development expert and consultant with 40 years of experience in these areas. A copy of my current curriculum vitae is attached as Exhibit 1.

2. I hold a Ph.D. in Pharmacology from State University of New York (Downstate Medical Center) and an M.D. degree from the University of Miami Medical School from a specialized Ph.D. to M.D. program, and received additional medical training at Cornell Medical College, the University of California at San Francisco and Brown University Medical School.

3. I am currently an independent consultant on matters relating to clinical trials, drug development and regulatory affairs and a consultant to the pharmaceutical industry, hospitals and the U.S. military.

4. I have served as Senior Vice President of Scientific and Regulatory Affairs for the Pharmaceutical Research and Manufacturers of America (PhRMA), the US trade association for large research based pharmaceutical companies, and represented the U.S. pharmaceutical industry on the steering committee for the International Conference on Harmonisation.

5. I am Clinical Professor of Pharmacy Practice at the University of Minnesota and Adjunct Professor of Medicine and Clinical Professor of Pharmacy at the University of North Carolina in Chapel Hill and visiting professor at the University of Illinois Medical School.

6. I have authored 15 textbooks on clinical trial methodologies and the processes of drug discovery and development, which are considered standard textbooks in the industry.

7. I have worked for four major pharmaceutical companies in drug discovery, development and management in a wide variety of therapeutic areas, which has included management of projects with extended release products.

8. I was President and co-founder of Orphan Medical, Inc., a public pharmaceutical company that develops and markets important medical products for patients with uncommon diseases.

9. I was nominated by the American Medical Association to be FDA Commissioner and I have received the FDA Commissioner's Special Citation for work in the orphan medicine area.

10. I have been asked to provide my expert opinion regarding the meaning of the term "with diminished incidence(s) of nausea and emesis" and "therapeutic metabolism" as a person of ordinary skill in the art in the mid-1990's would understand these terms from reading U.S. Patent No. 6,274,171 (the "'171

patent"), U.S. Patent No. 6,403,120 (the "'120 patent"), and U.S. Patent No. 6,149,958 (the "'958 patent"). I have reviewed Judge Martini's Markman Opinion from *Wyeth v. Teva Pharmaceuticals* in the District Court for the District of New Jersey and expert reports and declarations submitted in that case. I have reviewed the proposed claim constructions of Impax and Wyeth.

PERSON HAVING ORDINARY SKILL IN THE ART

11. For purposes of this Declaration, I assume a person having ordinary skill in the art is a person with at least a bachelors degree in pharmacy or some closely related discipline; at least two years of work experience or skill in the formulation, design, or evaluation of pharmaceutical dosage forms, including extended release dosage forms; and would have taken courses in both pharmacokinetics and pharmacodynamics or would have acquired comparable knowledge through work experience. Such a person would also have a working knowledge of, or would be able to consult as necessary with persons with expertise in (1) the pharmacologic profile, mechanism of action, and efficacy and adverse effects of serotonin, norepinephrine, and dopamine reuptake inhibitors in the treatment of psychiatric disorders, (2) the diagnosis and treatment of patients with psychiatric disorders, and (3) biostatistics.

REPRESENTATIVE ASSERTED METHOD CLAIMS

12. Claims 20, 22 and 23 of the '171 patent, claims 1, 2, 13 and 14 of the '120 patent and claims 1, 3 and 4 of the '958 patent require a "diminished incidence of nausea and emesis." The following claim is representative:

> 20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said

formulation containing venlafaxine hydrochloride as the active ingredient.

'171 Patent, Col. 12, line 63 – Col. 13, line 3.

INCIDENCE

13. "Incidence" is a term of art in clinical trial methodologies. Persons having expertise in clinical trial methodologies would read this term in the patents-in-suit to mean the number of patients who experience an event. People learn the meaning of this term from basic lectures and courses in statistics, in FDA guidances, in books on drug development, and in discussions about clinical trial design and interpretation of results. This term is used in the majority of clinical trials, as it can apply to many different aspects of a trial. I am not aware of any occasion when it had a different meaning, such as level; and, in reviewing approximately five different medical dictionaries never saw any definition that would relate to level. Level is synonymous with severity or intensity of an adverse event and it is categorically a different parameter than incidence. "Incidence" does not include consideration of the level, severity or duration of an event.

14. An adverse event is usually characterized by several different and distinct criteria: the incidence (number or rate) of patients in which it occurs, the level (intensity or severity) of its occurrence, whether or not it is related to the drug treatment, whether it meets the FDA definition of serious, and whether it requires an expedited report to the FDA and possibly the Institutional Review Board. Incidence and level are not used to describe the same characteristics of an adverse event.

15. A person of ordinary skill in the art would understand the patents-in-suit to show the aforementioned definition of "incidence." The patents state

that the claimed invention "provides a lower incidence of nausea and vomiting than the conventional tablets." '171 patent, Abstract. A person of ordinary skill in the art would understand that the claimed extended release formulation is purported to have a "diminished incidence of nausea and emesis" compared to the conventional formulation. The only discussion in the patents of the incidence of nausea associated with the conventional formulation concerns the percentage of patients who experienced nausea and vomiting while on the multiple daily dosing regimen:

> With the plural daily dosing regimen [immediate release], the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients. '171 patent, col. 2, lines 7-11.

Therefore, a person of ordinary skill in the art would understand the claim term "with diminished incidence[s] of nausea and emesis" in the patents to mean a decrease in the number of patients who have nausea and vomiting compared to those patients receiving the same total daily dose of an immediate release formulation that is administered two or more times a day.

16. To confirm my interpretation of "incidence," I looked at standard treatises and references in the fields of medicine, clinical trials, statistics and public health. All of these references are consistent with the definition of "incidence" discussed above:

- David Worthington, Dictionary of Environmental Health, Spon Press (2003), Exhibit 2 at 139 ("**incidence** The number of new cases of a disease, usually expressed as a RATE, occurring in a defined population within a specified time frame.").
- Beth Dawson et al., Basic & Clinical Biostatistics, Lange Medical Books/McGraw-Hill (4th Edition 2004), Exhibit 3 at 407 ("**incidence** A rate giving the proportion of people who develop a given disease or condition within a specified period of time.").

- Brian S. Everitt et al., The Encyclopaedic Companion to Medical Statistics, Hodder Arnold (2005), Exhibit 4 at 168 ("**incidence** The incidence of a disease is the number of new cases of the disease occurring within a specified period of time in a defined population.").
- Herman Koren, Illustrated Dictionary and Resource Directory of Environmental & Occupational Health, CRC Press (2d Edition 2005), Exhibit 5 at 331 ("**incidence** – (*epidemiology*) The number of cases of disease, infection, or some other event having an onset during a prescribed period of time in relation to the unit of population in which they occur.").
- Christopher J. L. Murray et al., Global Health Statistics: A Compendium of Incidence, Prevalence and Mortality Estimates for Over 200 Conditions, World Health Organization (1996), Exhibit 6 at 49 ("*Incidence*: this indicator measures the occurrence of new cases of disease or injury…").

THERAPEUTIC METABOLISM OF PLURAL DAILY DOSES

17. Several claims of the patents-in-suit use the phrase "therapeutic metabolism of plural daily doses." Claim 24 is representative:

> 24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. '171 Patent, col. 14, lines 5-13 (underline added).

18. In the context of the claim and the specification, the phrase "therapeutic metabolism of plural daily doses" is unknown to me as a term of art. While the terms "therapeutic" and "metabolism" each have clear meanings, the combination of the two words is not commonly used by persons of ordinary skill in the art, nor is it clear in the context of the claim or specification what is meant by "therapeutic metabolism of plural daily doses." The phrase "therapeutic metabolism of plural daily doses" is not described in the specification and its meaning remains unclear.

19. Looking at the entire preamble to Claim 24, "A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride...," a person of ordinary skill in the art would understand this to mean that the troughs and peaks due to the unspecified "therapeutic metabolism of plural daily doses" is eliminated by dosing only once per day. Generally speaking, there are two peaks and two troughs in a patient's blood plasma concentration when a drug is given twice a day, but a drug that is given once a day would only have one peak and one trough.

20. Therefore the preamble does not provide any insight as to the specific shape of "a graph of venlafaxine blood plasma concentration over time" (as proposed by Wyeth in its construction), other than eliminating a trough and a peak for a twice-a-day dose as described in the preceding paragraph. The preamble language does not tell a person of ordinary skill in the art either the slope or shape of the blood plasma curve over time. In addition, it does not provide any information on the magnitude of that curve, whether the magnitude of the troughs or peaks change with respect to the once a day or plural daily doses, or whether the troughs or peaks are sharp or more moderate.

CONCLUSION

21. Therefore the definition of incidence is unequivocally a number or rate of patients, in this patent and in the medical literature. It is clear that it does not include level, degree or severity as proposed by Wyeth.

22. The term "therapeutic metabolism" as used in Claim 24 is unclear because it is not commonly used by persons of ordinary skill in the art, nor is it defined or used in the specification of the patents.

23. I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct and that this declaration was executed on this 8 day of May, 2007 at Bethesda, Maryland.

Date: 5/8/07

By: _____
Bertram A. Spilker, M.D., Ph.D., F.C.P., F.F.P.M.

EXHIBIT 1

BERTRAM A. SPILKER, PhD, MD, FCP, FFPM

CONSULTANT

ADDRESS:	8004 Overhill Road, Bethesda, Maryland 20814-1145
TELEPHONE:	301-718-5150 (office)
FAX:	301-657-1403 (home)
E-MAIL:	bspilker@comcast.net

DATE OF BIRTH:	July 3, 1941, Washington, D.C.
MARITAL STATUS:	Married, Arlene Titow in 1967
CHILDREN:	Adam (born 1969) and Karen (born 1971)

EDUCATION:

University of Pennsylvania	A.B. in Chemistry	(1962)
State University of New York Downstate Medical Center	Ph.D. in Pharmacology	(1967)
University of California Medical Center at San Francisco	Post-Doctoral Research	(1968)
University of Miami Medical School Ph.D. to M.D. Program	M.D.	(1977)
Brown University Medical School Roger Williams General Hospital	Resident in Medicine	(1978)

MEDICAL LICENSES: North Carolina and Virginia.

MEDICAL PRACTICE: Part-time in Internal Medicine, Reston, Virginia (1978-1979).
Hypertension Clinic at UNC's Memorial Hospital, Chapel Hill (1980-1983).

HONORS:

Elected as Fellow of the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom (F.F.P.M.).

Elected as Fellow of the American College of Clinical Pharmacology (F.C.P.).

Proposed by the American Medical Association (AMA) to the Department of Health and Human Services (HHS) to be Commissioner of the FDA (1990).

FDA Commissioner's Special Citation for work on Orphan Drugs (1993).

Award of Excellence in Clinical Research (1993). Presented by Advanstar Publications, (1994). (First Annual Award).

Honorary Lifetime Membership in the American Academy of Pharmaceutical Physicians for contributions to pharmaceutical medicine (1994).

August, 2003

PAST POSITION:
1998-2002

Senior Vice President of Scientific and Regulatory Affairs,
Pharmaceutical Research and Manufacturers of America (PhRMA).

- Manage all issues concerning science and regulatory affairs
- Lead group of ten staff and oversee six steering committees (Regulatory, Clinical, Biotechnology & Biologics, Technical, Informatics and Preclinical) and 52 other committees with company members.
- Present technical expertise and reports as appropriate to Board of Directors and other PhRMA groups plus our member companies and other external organizations.
- Help develop PhRMA policy and present our position through multiple channels including public hearings and Congressional testimony.
- Provide media interviews 4-8 times each week to major media.
- Member of ICH Steering Committee and Co-Chair of the ICH Global Cooperation Group.
- Member, Institute of Medicine Roundtable on Drugs, NIH Panel on Surrogate Endpoints, and National Patient Safety Foundation Committee on Safe Drug Use Steering Committee (Represent the pharmaceutical industry).
- Maintain liaison and relationships with over 50 government agencies, professional groups and trade associations.

SUMMARY OF POSITIONS:

2002- Present	Bert Spilker & Assoc.	President
1998 - 2002	PhRMA	Senior Vice President
1994 - 1997	Orphan Medical	President
1993 - 1994	Chronimed	Executive Dir. of Orphan Medical
1993 - 1994	Chronimed	Vice President
1983 - 1993	Burroughs Wellcome	Director of Project Coordination
1979 - 1983	Burroughs Wellcome	Senior Clinical Research Scientist
1978 - 1979	JRB Associates	Senior Medical Consultant
1972 - 1975	Sterling-Winthrop	Senior Research Scientist
1970 - 1972	Philips-Duphar	Senior Research Scientist
1969 - 1970	Pfizer	Senior Research Scientist

PAST POSITION
1994 - 1997:

President
Orphan Medical, Inc.
Minnetonka, Minnesota 55305

The blueprint I created in co-founding Orphan Medical focused on licensing in drugs in Phase II with high medical value that could be developed rapidly at low cost (under $5 million) and would have an IRR above 40%.

I conducted all in-licensing to build the portfolio, created the development and regulatory strategies, recruited the staff, built the infrastructure of the company and managed the development program. A few highlights as of December 1997:

- Orphan Medical grew from a one person division to an independent public company on the major NASDAQ exchange.
- The staff grew from one to thirty-three.
- Five NDAs plus a 510k were filed and approved (Four methyl pyrazole for both human and veterinary use, Elliotts B solution, Betaine, Sucrase, Catrix). Another NDA was close to filing and has since been approved (i.v. Busulfex for bone marrow transplants).
- Twelve drugs were in development and 12 INDs active when I went to PhRMA in Washington, DC
- Held 28 face-to-face meetings with the FDA where we had remarkable success convincing them to accept novel development programs
- The market cap was $45 million (peaked at $70 million) (December, 1997)
- Raised a total of $29 million in two secondary IPO financings. Helped create the prospectus and was the main speaker on the "road shows"
- Received four FDA grants totaling almost $2 million
- Formed numerous alliances with marketing partners, both in the US and overseas
- Received the corporate award from the National Organization for Rare Disorders (NORD)
- Clinical trials were underway at over 80 sites (December, 1997)
- Obtained 12 US patents, 8 orphan drug designations, and 2 orphan drug status for our products

PAST POSITION
1993 - 1994:

Executive Director
Orphan Medical, a Division of CHRONIMED, Inc. &
Corporate Vice President, CHRONIMED, Inc.
Minnetonka, Minnesota 55305

Established, developed, staffed, and managed an organization that licensed in and developed products for orphan populations. During the 18 months that Orphan Medical was a Division of Chronimed, we had one OTC medicine brought to the market, seven prescription medicines licensed in and in development, staff was built from one to 12, and the division became an independent corporate entity.

PAST POSITION:
1983 - 1993

Director, Project Coordination
Burroughs Wellcome Co.
Research Triangle Park, North Carolina 27709

RESPONSIBILITIES:

Supervised the twelve staff members of the Department of Project Coordination; Lead the matrix project system; Provided assistance to all project leaders and managers; Directed 26 Therapeutic Area Panel Committees; Interacted with managers in Canada, Europe, and Japan to expedite drug development; Coordinated all licensing opportunities within research and development; Organized and planned major research and development meetings, including US-UK retreats and strategy meetings, Trustee visits, Research Committee, and informal U.S. strategy meetings; Spoke at in-house meetings to present the annual summary of research and development project activities (e.g. Burroughs Wellcome Canada, Corporate Affairs Unit, Human Resources Unit); Hosted

visiting dignitaries (e.g. Head of USSR Institute of Economics, Member of Central Presidium of Czechoslovakia, KABI Board of Directors).

ACCOMPLISHMENTS AT BURROUGHS WELLCOME CO.:

I. Medical Department

1. Designed, implemented, monitored, and interpreted data for a variety of significant Phase I to III clinical studies in neurology (e.g., epilepsy, Parkinson's Disease, centrally acting muscle relaxant for back pain).

2. Acted as principal investigator of two double-blind dermatology studies utilizing novel methodologies I developed.

3. Served as project leader for a centrally acting muscle relaxant.

4. Developed formats used for NDA reports on a neuromuscular blocking drug.

II. Department of Project Coordination

1. Organized the Department of Project Coordination and served as its first head from 1983 to 1993.

2. Supervised the creation and issuance of more than 20 new project-related documents and analyses that have been issued periodically since 1983.

III. Research, Development, and Medical Unit

1. Represented the Vice-President of Research, Development, and Medical at meetings and speaking engagements.

2. Modified the project system to strengthen it and improve its efficiency.

3. Created many analyses of the research and development function, including financial analyses.

4. Served as facilitator to help resolve differences between U.S. and U.K. departments.

5. Helped create and direct strategies on many projects.

6. Created the overall strategy document for research and development.

7. Created the research forum as a means to explore areas for future research.

8. Established and directed a multi-faceted educational program for project leaders.

9. Organized Burroughs Wellcome's overall strategy and specific programs for orphan drugs and quality of life activities.

10. Developed the program to create both proactive and reactive research and development strategies for licensing in new drugs.

11. Initiated a series of lunchtime seminars and panel discussions.

IV. Corporate Level

1. Served on corporate task forces representing research and development: security, strategy development, business principles, employee drug testing, licensing activities.

2. Instituted a project manager system for supervising OTC drug projects.

3. Represented research and development in creating the overall Burroughs Wellcome Co. strategy document.

4. Reviewed licensing proposals and participated on decision making panels.

V. Worldwide Wellcome Foundation

1. Organized and participated in annual retreats and meetings each year, including the main international retreat for research and development at which the UK and US CEOs and marketing heads attended.

2. Prepared speeches for the Vice-President of Research, Development and Medical, and the Chairman of the Wellcome Foundation. Wrote sections of the annual report.

3. Co-authored the first worldwide research and development strategy document and participated in the creation and review of others.

4. Developed many procedures used internationally between research and development and marketing units, and within research and development.

PREVIOUS POSITION: 1979 -1983

Senior Clinical Research Scientist
Department of Clinical Research
Burroughs Wellcome Co.

Responsible for the design and analysis of clinical trials that were implemented through investigators in North America. These were in the area of epilepsy, Parkinson's Disease and other therapeutic areas. Served also as project leader.

ACADEMIC APPOINTMENTS: (At Present)

Adjunct Professor of Medicine (1980 - present)
Department of Medicine
University of North Carolina Medical School

Treated patients in the Anti-Hypertension Clinic (1980 to 1983). Participated in research projects and presented lectures (1979 to 1993). Promoted from Clinical Assistant Professor to Clinical Associate Professor (1988), and to Full Professor (l990).

Clinical Professor of Pharmacy (1980 - present)
University of North Carolina School of Pharmacy

Presented an entire 28-hour course on advanced methods in clinical studies (1988). Presented lectures in various other courses each year from l980 to l992).

Clinical Professor of Pharmacy Practice (1993 - present)
University of Minnesota School of Pharmacy

Presented lectures and seminars in various courses (l993 to l998).

Clinical Professor in the Graduate Faculty of Social and Administrative Pharmacy
University of Minnesota School of Pharmacy

Presented lectures and seminars in various courses (1993 to l998).

Visiting Professor of Clinical Pharmacology
University of Illinois Medical School, Peoria, Illinois (1995 - 2005)

Presented course on clinical trials (1996).

ACADEMIC APPOINTMENTS: (Previous)

Adjunct Professor of Business (1992)
Fuqua School of Business
Duke University
Durnham, North Carolina

Co-taught a course on the pharmaceutical industry with Professor Henry Grabowski, Chair and Professor of Economics.

Adjunct Professor of Pharmacology (1979 - 1996)
Department of Pharmacology
University of North Carolina Medical School

Presented lectures to graduate students in several courses (1980-1993). Promoted from Adjunct Associate Professor to Full Professor (1988).

BOARD OF DIRECTORS: (Previous)

Swedish Orphan A.B. (Stockholm), 1990 - 1993
Orphan Europe S.A.R.L. (Paris), 1990 - 1993
Multimedia Publishers (New York), 1994 - 1995
Society for Chronic Disease (Minneapolis), 1993 - 1997
Orphan Medical, Inc. (Minnetonka), 1994 - 1997
MetaWorks, Inc. (Boston), 1996 - 1999
Phoenix International Life Sciences (Montreal), 1997 - 2001

SCIENTIFIC ADVISORY BOARDS:

MetaWorks Inc. (Boston), 1993 - 1996
United States Pharmacopeia (Rockville, MD), 1995 - 1997
(Represented the American Medical Association)
DataEdge, Inc. (Philadelphia), 1995 - 2001
Centre for Medicines Research (Epsom, UK), 1999 - 2002
UNC-CH (Chapel Hill, NC) Center for Education and Research in Therapeutics (CERTS), 1999 - present
Acurian Inc. (Philadelphia), 2000 - present
LearnWright (Rockville, MD), 2001 - present
Fast Track (San Mateo, CA), 2001 - present
Ernst & Young (McLean, VA), 2001 - present
Madison Avenue Tools (Milwaukee), 2001 - 2004

PAST POSITIONS:
1978 -1979

Senior Medical Consultant
JRB ASSOCIATES, INC., 8400 Westpark Drive, McLean, Virginia 22102. Telephone (703) 821-4866

JRB Associates, Inc. employed more than 200 professionals in all aspects of health related services.

Selected projects in which I participated:

1. The National Cancer Institute (NCI)

Directed the activities of 15 professionals who analyzed, classified, and evaluated the entire archive of Public Health Service documents related to low-level radiation resulting from atomic weapons testing in the 1950's and 1960's. Served as advisor and staff director to a national panel of experts established by the Secretary of Health, Education, and Welfare to recommend future research objectives with respect to low-level radiation.

2. The Environmental Protection Agency (EPA)

Under the Toxic Substance Control Act, the EPA identified 11 groups of chemicals to be evaluated in order to determine their potential for causing health problems. I reviewed and evaluated the human health data for several of these groups of chemicals and provided recommendations for future clinical investigations.

3. The Food and Drug Administration (FDA)

JRB provided economic and legislative analyses related to the Drug Regulation Reform Act and the Medical Device Amendments of 1976. I served as task leader for the former project and evaluated clinical investigations of medical devices for the latter.

PREVIOUS PHARMACEUTICAL EXPERIENCE:
1969 -1970

Pfizer Ltd.
Sandwich, Kent, England

Personally established and directed the Cardiac Stimulant program with a staff of six to study drugs acting on heart muscle, and organized the laboratories to carry this out.

Collaborated on the animal research of Prazosin (Minipress), a new antihypertensive.

Collaborated on the animal research of Tolamolol, a new beta adrenergic antagonist.

Developed the structure activity relationship that directly led to the development of a new drug for the treatment of heart failure. This drug was tested in clinical trials.

1970 -1972 Philips-Duphar B.V.
Weesp, The Netherlands

Personally established and directed the antithrombotic and antihypertensive program with a staff of six, and organized the laboratories to carry this out. Collaborated on the animal research of Tiprenolol, a new beta-adrenergic antagonist.

Collaborated on the animal research of Ritodrine, a beta-adrenergic agonist used to retard premature labor.

1972 -1975 Sterling-Winthrop Research Institute
Rensselaer, New York

Directed the Bronchodilator and Autonomic Pharmacology Projects. Responsible for: hiring, training, supervising, and evaluating seven employees.
Performed many of the animal studies on the bronchodilator Bitolterol, (Tornalate).
Collaborated on Phase IV Isoproterenol (Isuprel) and Isoetharine (Bronkosol) studies.

TEACHING EXPERIENCE:

Downstate Medical Center - Department of Pharmacology
Lectured and led laboratory sections. (1965-1967).

University of California Medical Center
Taught an eight-lecture course in pharmacology. (1967-1968).

Pfizer, Ltd.
Advisor to two graduate students. (1969-1970).

University of North Carolina Medical School
Taught cardiovascular pharmacology to graduate students, supervised clinical pharmacology laboratories for medical students, and lectured to medical students. Served as Masters thesis advisor for a student in the School of Pharmacy. Lectured in several different courses each year from 1979 - 1993.

Duke University Fuqua School of Business
Taught a course on the pharmaceutical industry with Professor Henry Grabowski. (1992).

University of Illinois College of Medicine at Peoria
Taught a 16-hour course on topics related to clinical trials. (1996).

University of the Sciences in Philadelphia
Taught a two-day course in drug development (2002 to 2005)

Tufts University Center for the Study of Drug Development
Taught two lectures on clinical trials (2004, 2005)

COURSES:

Created the three day course "Clinical Interpretation of Drug Data" (1985) and served as Course Director at the Center for Professional Advancement.

Presented the above course twice each year in the United States and once each year in The Netherlands (1986 -1990). Also presented this course in Denmark (1988).

"Practical Aspects of Clinical Trials and Strategies"
I presented this two or three-day course:
Copenhagen (1989)
Uppsala, Sweden (1990)
Washington, DC (1990)
London, (1991)
Barcelona, (1992)
This was presented as a one-day course in Denmark (1993).

"Improving Your Effectiveness as a Pharmaceutical Manager"
I presented this two-day course:
London (1990)
Madrid (1991)
Paris (1991)

"Symposium on Clinical Trials"
I presented most of this two-day course in Pretoria, South Africa (1992).

PROFESSIONAL SOCIETIES:

American College of Clinical Pharmacology (ACCP) - Fellow (FCP)
American Management Association (AMA)
American Medical Association (AMA)
American Society for Pharmacology and Experimental Therapeutics (ASPET)
American Society for Clinical Pharmacology and Therapeutics (ASCPT)
Drug Information Association (DIA)
Society for Clinical Trials (SCT)
Society for Pharmaceutical Medicine (SPM)

EDITORIAL WORK:

Editorial Board of:
"American Journal of Clinical Research" (1992 through 1996).
"Clinical Research and Drug Regulatory Affairs" (1987 through 1991).
"Drug Information Journal" (1989 through 1991).
"Drug News and Perspectives" (1988 to present).
"Quality of Life Research" (1991 to present).
"Applied Clinical Trials" (1992 to 2002).

Review journal manuscripts for:

"JAMA", "European Journal of Pharmacology," "Archives Internationales de Pharmacodynamie et de Therapie," "Journal of Investigative Dermatology," "Epilepsia," "Controlled Clinical Trials," "Medical Care," "Journal of Clinical Epidemiology," "PharmacoEconomics", "Cancer" and others.

Review guidelines for:
World Health Organization

Judge for:
First Annual SCRIP Awards for Pharmaceutical Companies, 2005

BIOGRAPHICAL LISTINGS:

American Men and Women of Science
Dictionary of International Biography
International Who's Who
Men of Achievement
Personalities of America
Personalities of the South
Who's Who in Frontier Science and Technology
Who's Who in Society

PROFESSIONAL ASSOCIATIONS:

Pharmaceutical Manufacturers Association (PMA)

Member of PMA Commission on Drugs for Rare Diseases (1988 - 1990).
Chairman of PMA Commission on Drugs for Rare Diseases (1990 - 1993).
Member of Medical Relations Committee (1986 - 1989).
Co-Chair of Medical Relations Committee (1989 - 1992).
Chair of Medical Relations Committee (1992 - 1993). Chair of the Task Force on forming the American Academy of Pharmaceutical Physicians (1991 - 1993).

PMA Visiting Scientist at Schools of Pharmacy:

University of Nebraska (1986)
Creighton University (1986)
University of Minnesota (1987)
University of Alberta (1988)
University of Saskatchewan (1988)
Ohio Northern University (1989)
Auburn University (1990)

Founded the Visiting Industry Program for Physicians at Medical Schools.

PMA Medical Section Meeting Talks and Panel Presentations
"Problems with Multinational Versus Uninational Clinical Trials." (1990).
"Design, Conduct, and Analysis of Data from Clinical Trials in a Harmonized World." (1990).
"Pharmaceutical Industry Perspective on Orphan Medicines." (1991, 1992).

"Report of the Task Force on an Association of Pharmaceutical Physicians." (1991, 1992).
Many additional presentations made at meetings from 1987 - 1993, and at PhRMA meetings from 1998 to present.

Pharmaceutical Manufacturers Association of Canada
Presented a one-day series of talks and workshops on drug development topics in Montreal (1989) and in Toronto (1989, 1992, 1993, 1994).

Proprietary Association (PA)
Member of Antirheumatic Task Group (1986 - 1990).

American Cancer Society
Liaison Member, Committee on Clinical Trials (1988 - 1992).

Swedish Institute of Health Economics and Danish National University
Presented lectures and workshop on quality of life in Copenhagen (1993, 1994, 1995).

Pharmaceutical Education and Research Institute (PERI)
Presented over a dozen lectures and talks through 2000.

KEYNOTE ADDRESSES:

"An Overview of Clinical Investigations." Regulatory Affairs Professionals Society, San Diego (1989).

"Trends and Forces in the Pharmaceutical Industry and Their Impact on Information Management." Drug Information Association, Philadelphia (1990).

"Future Directions of Clinical Trials and Strategies." First Annual Clinical Research and Practice Conferences, Auburn University School of Pharmacy, Auburn, Alabama (1990).

"An Overview of the Factors Influencing Innovation." at the Conference: Creating the Research Environment for Drug Discovery, Centre for Medicines Research, London (1990).

"Multinational as Opposed to Uninational Clinical Trials." South African Pharmacology Congress, Bloemfontein (1992).

"Principles of Clinical Audit and How to Prepare for an Audit by the FDA." South African Pharmacology Congress, Bloemfontein (1992).

"Standards for Quality of Life Trials." South African Pharmacology Congress, Bloemfontein (1992).

"Ethical Issues in Clinical Trials." South African Pharmacology Congress, Bloemfontein (1992). "Standards for Clinical Trials & Medical Devices." Medical Alley, Minneapolis (1993).

"Standards of Clinical Trials for Medical Devices." Bethesda (1994).

"Virtual Drug Development on a Global Basis." Spanish Pharmaceutical

Physicians, Barcelona (1996).

"Clinical Investigations: An Overview of Where We are Going in the '90s." Regulatory Affairs Professionals Society, Washington DC (1996).

"Uses and Misuses of Quality of Life Data." International Epilepsy Congress, Dublin (1997).

"Recruitment and Retention Strategies in the New Millennium." Halifax (1998).

"Post Marketing Surveillance in the New Millennium: Practices and Challenges" Opening Ceremony of New Clinical Research Unit of Seoul National University", Seoul (1998).

"Current Trends in the Pharmaceutical Industry that Impact International Commerce" Cosmos Alliance, Washington (2003).

"Pharmaceutical Opportunities and Directions" Prous Science Users Meeting, Princeton and San Diego (2003).

"Current Trends in Drug Development" PhRMA's Annual Meeting of the Biomedical Compliance Committee, Bethesda (2003).

"Advancing Clinical Research in Otolaryngology Through Industry Partnerships" Neel Distinguished Research Lecture, ENT Society, Orlando (2003)

"The Successful Management of Clinical Trials: The Good, The Bad and The Ugly" Association of Clinical Research Professionals, Paris (2005)

INVITED LECTURES AT UNIVERSITIES:

"Clinical Pharmacology in the Drug Industry." Department of Pharmacology, University of North Carolina Medical School, Chapel Hill (1981).

"Practical Considerations in Planning and Conducting Clinical Trials." Department of Pharmacology, University of North Carolina Medical School, Chapel Hill (1983).

"Myths and Misconceptions About the Drug Industry Today." Symposium: "Business Ethics in the Drug Industry" at East Carolina University, Greenville, North Carolina (1984).

"The Golden Rules of Clinical Trials." Johns Hopkins Medical School, Baltimore (1988).

"Interpretation of Clinical Data." University of Montreal, Montreal (1989).

"Ethical and Policy Issues of Government Regulations for Anti-AIDS Drugs." Institute of Policy Sciences and Government Affairs, Duke University, Durham (1990).

"Academic-Industry Relationships." AAMC Meeting, Duke University, Durham (1990).

"Quality of Life Assessments in Clinical Trials." Yale University, New Haven (1990).

"Cross-Cultural Functioning: Issues and Resolutions." Distinguished Lecture Series at the University of North Carolina, Chapel Hill (1990).

"Designing and Implementing Research Protocols in Clinical Departments." Albany Medical College Grand Rounds, Albany (1990).

"Perspectives on Quality of Life Issues." Health Policy Forum of the University of North Carolina School of Public Health (1991).

"The Medical and Marketing Interface in the Pharmaceutical Industry." University of Mississippi, Oxford (1991).

"Current Issues in the Pharmaceutical Industry." Duke University (1992).

"Roles of Statisticians in Clinical Research." Medical Research Council of South Africa, Pretoria, South Africa, Pretoria, South Africa (1992).

"Patient Compliance in Clinical Trials." University of Durban - Westville, South Africa (1992).

"Current Issues in Clinical Trials." Medical Research Council of South Africa, Capetown, South Africa (1992).

"Marketing Less Commercially Attractive Drugs." University of Minnesota (1993).

"Forum on Drug Development and Clinical Trials." Philadelphia College of Pharmacy and Science (1993).

"Orphan Drug Development." University of Minnesota Pharmacy Honor Society Awards Banquet (1995).

"Centralized Clinical Trials in a University Hospital Setting." University of Cincinnati, Grand Rounds (1996).

"The Value of Clinical Trials in Pediatrics." University of Michigan Medical School, Grand Rounds (1997).

"Golden Rules of Clinical Drug Development." Seoul National University Special Seminar (1998).

"Roles of Regulatory Affairs Professionals." Seoul National University Special Seminar (1998).

"Good Clinical Research Practices." Johns Hopkins University Medical School (1999).

"Are FDA Standards of Drug Safety Appropriate?" Johns Hopkins University Medical School (1999).

"Current Topics in Pharmaceutical Development" University of Florida School of Pharmacy (2002).

INVITED LECTURES AT PROFESSIONAL MEETINGS:

"Changing Regulations with Special Reference to the Drug Regulation Reform Act." ASCPT Symposium: "Forces Altering Clinical Trial Design." in San Francisco (1980).

"Approaches to Cooperation on the Discovery of New Therapies for Rare Disorders." Mount Sinai Medical School, New York (1984).

"Development of Orphan Drugs: An Industry Perspective." Conference of "Orphan Drugs and Orphan Diseases" Leeds Castle, England (1985).

"An Industry Perspective on Orphan Drugs." at the "National Conference on Orphan Drugs" Washington, D.C. (1988).

"Drug Development: An Industry Perspective." Family Health International, Research Triangle Park, North Carolina (1988).

"Postmarketing Standards." Regulatory Affairs Professionals Society, Nice, France (1989).

"Future Directions of Clinical Trials and Strategies." Drug Information Association, Boston (1989).

"Visiting Scientists Program in Schools of Pharmacy." American Association of Colleges of Pharmacy, National Meeting, Portland (1989).

"The Future of Medicines." World Conference on the Future, Washington, D.C. (1989).

"Design of Studies to Measure and Enhance Compliance." Drug Information Association Workshop, Philadelphia (1989).

"Planning and Managing Integrated Clinical Development Programs: Flexible Two Research Center Approach." Drug Information Association, Amsterdam, The Netherlands (1989).

"National Versus Multinational Clinical Trials: Impact of Medical, Cultural, and Regulatory Differences." Drug Information Association, Amsterdam, The Netherlands (1989).

"The Future of Drug Discovery and Development." American College of Physicians, Chicago (1990).

"How to Conduct More Clinical Trials With Fewer Resources." Seventh International Conference on Pharmaceutical Medicine, Madrid (1990).

"How Can the Standards of Published Clinical Trials Be Improved." Seventh International Conference on Pharmaceutical Medicine, Madrid (1990).

"Extrapolation of Preclinical Safety Data to Humans." Canadian Public Health Association and World Health Organization Symposium on Risk Estimation for Pharmaceuticals, Ottawa (1990).

"Partnering Initiatives to Increase Product Value." Conference on Strategies in the Pharmaceutical Industry, New York (1991).

"The Pharmaceutical Industry's Response to the New Orphan Drug Regulations." Food and Drug Law Institute Seminar, Washington, D.C. (1991).

"The Perspective of the Pharmaceutical Industry on Orphan Drugs." National Organization of Rare Disorders First Annual Meeting, Baltimore (1991).

"External Influences on Protocol Design." Antiepileptic Drug Trials Workshop, Miami (1992).

"Health Related Quality of Life." Quantitative Assessment of Epilepsy Care, (NATO sponsored meeting) Porto, Portugal (1992).

"Worldwide Compatability of Diagnostic Criteria." Drug Information Association, San Diego (1992).

"Roles of Regulatory Affairs in Drug Development." Drug Information Association, San Diego (1992).

"Pharmacoeconomics." Capitalizing on Healthcare Reform, Chicago (1993). "Benefit to Risk Considerations in Drug Development." Drug Information Association, London (1993).

"Drug Development Under Health Care Reform." Drug Forum, Tokyo (1993).

"Valuing a Deal from Both the Licensor's and Licensee's Perspectives." Global Business Research Meeting, San Francisco (1994).

"Patient Recruitment in Clinical Trials." New Clinical Drug Evaluation Unit (NCDEU) Meeting, Marco Island, Florida (1994).

"Standards of Clinical Trials for Medical Devices," Bethesda, Maryland (1994).

"Orphan Drug Development – Lessons for Europe." Geneva Pharmaceutical Consortium, Geneva (1996).

"Orphan Drug Development on a Global Basis." Management Forum, London (1996; 1997).

"Perspectives for Viewing Quality of Life and Pharmacoeconomics." American Association of Pharmaceutical Scientists, Seattle (1996).

"What's New in Clinical Trials." Eighth Phoenix Symposium, Montreal (1997).

"Creating a Frame of Reference for Pharmacoeconomics." International Epilepsy Congress, Dublin (1997).

"Methods to Improve Patient Compliance." Drug Information Association, Baltimore (1997).

"Quality of Life Instruments: Statistical Issues." Swedish Statistical Society, Uppsala, Sweden (1997).

"Industry Views on Academic Freedom to Publish Research Data." Council of Scientific Society Presidents, Washington DC (1998).

"The Future of Pharmaceutical Spending." AAAS Workshop "How to Fund Science: The Future of Medical Research, Wye River MD (1999).

"Drug Safety." American College of Preventive Medicine, Crystal City VA (1999).

"Pharmaceutical Activities in Neuro-therapeutics." American College of Neuro-therapeutics First Annual Meeting, Washington DC (1999).

"Direct to Consumer Ads: An Industry Perspective." National Association of Boards of Pharmacy, Washington DC (1999).

"ICH Globalization Initiatives." ICH Conference, Washington DC (1999).

"Welcoming Address" ICH Fifth International Conference, San Diego, CA (2000).

"Global Cooperation Group" ICH Fifth International Conference Plenary Session, San Diego, CA (2000).

" Shortening Drug Development" Health Pathways and Maryland High Tech Society Inaugural Speaker, Gaithersburg, MD (2003).

"Clinical Development Strategies" and "Regulatory Strategic Approaches." Each talk presented at a one-day Food and Drug Law Institute Conference in Washington, DC (2002) and in Teaneck, NJ (2003).

"Issues and Problems of Clinical Data Interpretation" 12th International Congress on Cardiovascular Pharmacotherapy, Barcelona, Spain, (2003).

"Approaches to Shortening Drug Development" Japanese Economic and Trade Organization, New York (2003).

" Investigator Sponsored Research: Pharmaceutical Industry Perspective" DIA Annual Meeting, Washington, DC (2004).

" Industry Perspective on Clinical Trial Registries" DIA Annual Meeting, Washington, DC (2005).

"A New Era for Safety and Pharmacovigilence" Association of Clinical Research Professionals, Paris (2005).

INVITED "Health Policy Issues Regarding Quality of Life." University of North

DISCUSSANT:

Carolina/Glaxo Symposium (1991).

"Statistical Analysis of Safety Data from Clinical Trials." Drug Information Association, Chicago (1993).

"Comments on Methodological Aspects of Proposed Trial of DCA in Cerebral Malaria." NIH, Bethesda (1993).

"Improving the Efficiency of Drug Development." at Pharmaceutical Executive Conference, New Brunswick (1994).

"Risk Communications" at Meeting co-sponsored by FDA, PhRMA and AHRQ , Chapel Hill, NC (2001).

"ICH Activities with Non-ICH Countries" (CIOMS - International Council of Medical Society Organizations), Geneva (2002).

"Industry's Perspective on Ethical Guidelines" at CIOMS, Geneva (2002).

MODERATOR OR SESSION CHAIR:

"The Future Starts Now-Geriatrics and Emerging Specialties." Research Triangle Park, North Carolina (1980).

"Update on Headaches." Research Triangle Park, North Carolina (1981).

"Practical Solutions for Common Medical Problems." Research Triangle Park, North Carolina (1984).

"New Concepts and Strategies for Clinical Trials." Drug Information Association, Boston (1989).

"National Versus Multinational Clinical Trials: Impact of Medical, Cultural, and Regulatory Differences." Drug Information Association, Amsterdam, The Netherlands (1989).

"Interpretation of Laboratory Data." Associates of Clinical Pharmacology, Montreal (1990).

"New Treatment of Rare Diseases." Frontiers in Rare Disease Research, Second Biennial Conference, Washington, D.C. (1990).

"FDA Regulations in the 1990s." Drug Information Association, San Francisco (1990).

"Improving Data Management and Use of Resources in Clinical Research." Seventh International Conference on Pharmaceutical Medicine, Madrid (1990).

"Managing Investigational Medicines More Effectively." Drug Information Association, Washington, D.C. (1991).

"Current Issues and Dilemmas in Quality of Life Trials." Clinical Research International Symposium, Washington, D.C. (1991).

"Clinical Trials.". Two-day Conference in Philadelphia (1992).

"Orphan Drug Development in Europe." One-day Conference in London (1996).

"Global Product Registration." Two-day Conference in Philadelphia (1996).

"Surrogate Endpoints." Half-day Meeting at NIH Meeting in Bethesda (1998).

"Methodology of Surrogate Endpoints." Breakout Chair at NIH Meeting in Bethesda (1999).

"Opening Plenary Session of ICH-5" Co-chair with Dr. Sharon Smith Holston, FDA. Three day meeting, San Diego, CA (2000).

"Plenary Session on Hepatotoxicity." Meeting sponsored by FDA, PhRMA and AASLD, Westfields, VA (2001).

"Risk Assessment." Meeting co-sponsored by FDA, PhRMA and AHRQ, Chapel Hill, NC (2002).

PRESENTATIONS TO GOVERNMENT:

Presentation to Korean FDA Commissioner on Ethnic Diversity Aspects of New Development (May 18, 1998).

Statement on IRBs to Government Reform and Oversight Subcommittee on Human Resources (House of Representatives) (June 11, 1998).

Seminars at FDA: Regulatory and Scientific Roles and Activities of PhRMA (June 24, 1998); Quality of Life Issues (December 4, 1998)

Statement at FDA CBER Stakeholder's Meeting (August 14, 1998).

Statement at FDA CDER Stakeholder's Meeting (August 17, 1998).

Statement at FDA Stakeholder's Meetings (September 14, 1998; April 28, 1999; August 6, 1999 (Dietary Supplements)).

"Conceptual Models of Surrogate Endpoints." Presentation at NICHD Workshops (1998, 1999); PPRU Workshop of NICHD (1999).

Seminar at the Armed Forces University of Technology on "Industry Views of Regulations (1999 and 2000).

Presentation to NIH Conference on Women's Health Issues (1999).

Presentation to NIH Conference on Surrogate Endpoints (1999).

GAO Conference on Drug Safety: Industry Perspective (1999).

Presentation to FDA's Office of Pharmaceutical Sciences (2000).

Presentation to FDA's Office of Orphan Products Development (2000).

Two statements to the FDA and NTSB on Drugs and Driving (2001).

Statement to the FDA's RX to OTC Hearing (2001).

Presentation to National Academy of Sciences on Industry's View of Medical Journal Policies (2001).

Presentations to the Institute of Medicine on Human Subject Protection (2001), and on Clinical Trials (2001).

GOVERNMENT CONSULTANT:

Chairman of the National Cancer Institute's (NCI) Special Review Committee of Grants for Quality of Life Assessments in Special Populations. Three day meeting in Columbia MD (1993).

National Institute of Drug Abuse (NIDA) meeting on Master Agreements (1993); grant reviews (1993, 1999).

Agency for Health Care and Policy Research (AHCPR) grant reviews (1999).

Member of the NIH "Ad Hoc Advisory Group on the Coordination of Rare Disease Research" (1997).

Special Adviser to the Head of NIH for the Road Map Project (2002-2003).

PRESENTATIONS TO CONSUMER GROUPS:

Consumer Federation of America: "Overview of Safety" (1998); Panel on Safety in the Modernized FDA (1999).

Consortium on Microbicides: Industry Perspective (1999).

MEETING ORGANIZER/ PLANNING COMMITTEE

American Enterprise Institute: Safety Meeting (1999).

IOM Pediatric Conference (1999).

NIH Surrogate Endpoint Meeting (1998 and 1999) - See book chapters F2, F3.

FDA, PhRMA, AASLD Hepatotoxicity Conference (2001).

FDA, PhRMA, AHRQ Risk Assessment Meeting (2002).

MEDIA PRESENTATIONS:

"Key Drivers for the 21st Century" National Press Foundation (Washington, DC, 1999).

CIVIC CLUB TALKS:

"Discovery and Development of New Drugs." Durham Rotary Club (1986); Chapel Hill Kiwanis Club (1986); Chapel Hill Rotary Club (1987); Raleigh Civitan Club (1987); Association of Extension Home Economists (1988); Raleigh Kiwanis Club (1989); Raleigh Rotary Club (1989); Raleigh Academy of

Medicine (1990); Durham Jaycees (1990); Rho Chi (Pharmacy Honor Society, 1995).

MARKETING TALKS: Training of Sales Representatives at the Burroughs Wellcome Company (1980 - 1992).

Formal discussions with 40 to 80 physicians in Johannesburg, Durban, and Capetown, South Africa (1992).

CAREER TALKS: Discussions with physicians who recently joined the industry.
PERI (Arlington, VA). 1998 (2x); 1999 (2x).

Talks at North Carolina Central University (Durham, NC). (1991-1992).

MANAGEMENT: Directed a staff of up to 30 (1993 - 2002).

Business courses at the State University of New York in Albany (1974) and University of North Carolina at Chapel Hill (1988).

Consultant to the UNC School of Business (1983 -1984).

INVITED REVIEWER:
Institute of Medicine Reports (1990 – 2001).
Grant Applications submitted to the Dutch National Cancer Society (1991).
Faculty Tenure Application - University of Toronto (1991).
National Institute of Drug Abuse Reports (1992 - 2001).
GAO Reports (1999 - 2001).
Inspector General Reports (1999 - 2001).
National Bioethics Advisory Board Reports (1999 - 2001).

ADDITIONAL INFORMATION: Collaborated with Dr. John Coltart at St. Bartholomews Hospital in London on research into electrophysiological effects of drugs (1969 - 1971).

Completed the Boston Marathon (1966).

Invited seminar speaker and course director at many major pharmaceutical companies (1983 to present).

Proposed the formation of a consortium on Rare Diseases in December 1990 to the Orphan Products Board of the Department of Health and Human Services (DHHS). This concept was approved by the Assistant Secretary of the DHHS in June 1991 and the meetings initiated later in 1991 with 24 representatives of government, academic, trade association, consumer, and industry groups.

Interim President of Phoenix, United States, a Canadian contract research organization (CRO) (January through March 1998). Led a staff of 330.

EXHIBIT 2

Y OF HEALTH
NT:

VTEC 0157
5235952
sing

igement
5
on
3
6th edition
0

ress

Toxic Cyanobacteria in Water
by Ingrid Chorus and Jamie Bartram
0419239308
grading Water Treatment Plants
len Wagner and Renato Pinheiro
419260404 HB, 0419260501 PB
Water Pollution Control
hard Helmer and Ivanildo Hespanhol
0419229108
Quality Assessments
Deborah Chapman
5 HB, 0419216006 PB
Quality Monitoring
and Richard Balance
HB, 0419217304 PB
affic Pollution
O. Zali 0419237208

DICTIONARY OF ENVIRONMENTAL HEALTH

David Worthington

Spon Press
Taylor & Francis Group
LONDON AND NEW YORK

First published 2003
by Spon Press
11 New Fetter Lane, London EC4P 4EE

Simultaneously published in the USA and Canada
by Spon Press
29 West 35th Street, New York, NY 10001

Spon Press is an imprint of the Taylor & Francis Group

Typeset in Times by Taylor & Francis Books Ltd
Printed and bound in Great Britain by The Cromwell Press,
Trowbridge, Wiltshire

British Library Cataloguing in Publication Data
A catalogue record for this book is available
from the British Library

Library of Congress Cataloging in Publication Data
Worthington, David, 1953–
Dictionary of environmental health / David Worthington.
(Clay's library of health and the environment)
Includes bibliographical references and index.
1. Environmental health–Dictionaries. I. Title. II. Series.
RA566.W68 2002
616.9'8'03–dc21 2002029208

ISBN 0–415–26724–2

Clay's Li
the

An increasing breadth a
threats of the environr
increasing sophistication

Clay's Library of Hea
publication of leading-ec
issues. The flagship publi
in its 18th edition, cont
professionals in over thir

Series Editor:
Bill Bassett: Honorary
Sciences, University of E
and Housing, Exeter Cit

Editorial Board:
Xavier Bonnefoy: Regic
Health, World Health O
Don Boon: Director of I
Borough of Croydon, Uk
David Chambers: Head
Michael Cooke: Environ
tant, UK, formerly Chief

am; the body does not de-
ity to produce these agents

ne phenomenon whereby an
protected from the effects of
nts or poisonous substances
otherwise result in illness.
ay be inherent within the
be developed or acquired
n response to infection or
IUNISATION. Immunity may
complete and may last for a
or for life.

ty Any form of analysis that
ecific reaction between an
id an ANTIGEN for the pur-
rentiation.

mpetent Refers to an indivi-
body is able to mount a
ane response.

MUNOCOMPROMISED

mpromised A condition in
dividual's immune system is
ount a normal response to the
ction. The condition can be a
nomenon, brought about by
induced during surgical pro-
h as transplant) in order to
possibility of rejection of the
organ.

V; IMMUNOCOMPETENT

bin One of a group of pro-
e ANTIBODIES. Their action is
c and usually limited to a
EN.

gical test An analytical test
d on the reaction between an
nd an ANTIGEN.

MUNOASSAY

agnetic separation An analy-
que used for isolating a specific
ism. It works through the use

of magnetic beads coated with the ANTIBODY to the organism being sought, against which the organisms form clumps.

immunosuppression The term usually used to describe the intentional medical intervention, especially through the use of drugs, of preventing the normal operation of the body's immune system in order to aid the acceptance of transplanted material.

immunotherapy A medical intervention intended to benefit a patient by the attenuation of the body's immune response mechanisms. Immunotherapy includes stimulating the immune system such as to attack pathogenic microorganisms and suppressing it such as to aid the acceptance of transplanted organs or other material.

imprest A cash fund or advance held by an individual or department for paying incidental expenses and that, following expenditure, is topped up periodically to a predetermined level.

in situ A Latin term meaning 'in the original situation'. It generally refers to an act of examination, maintenance or similar conducted without removing the object of the exercise from its location or environment.

in vitro A Latin term meaning literally 'in a glass'. It is applied to experimentation on living cells conducted outside the body, for example in petri dishes etc.

See also: CELL CULTURE; IN VIVO

in vivo A Latin term describing activity or observation that takes place within the living body.

See also: IN VITRO

incidence The number of new cases of a disease, usually expressed as a RATE, occurring in a defined population within a specified time frame.

See also: PREVALENCE

incidence rate *see* ATTACK RATE

incineration The process of burning waste under controlled conditions to either reduce its bulk or denature toxic or hazardous characteristics. The term usually refers to the process of direct incineration, in which the calorific value of the waste itself is utilised during burning. Direct incineration is often associated with production of heat or power. Variations of the incineration process are being developed in which the objective of heating the waste is not its direct incineration.

See also: ENERGY FROM WASTE; GASIFICATION; PYROLYSIS

income elasticity The proportionate change in an individual's lifestyle and/or health status produced by a proportionate change in that person's income.

incubation period That time between the initial invasion of a susceptible host by a PATHOGENIC organism and the first appearance of the clinical symptoms associated with the infection. In the majority of cases the incubation period is fairly consistent within a defined time scale, and knowledge of the organism, together with knowledge of the onset of symptoms, can be used as a retrospective indicator as to when the initial infection occurred. This is particularly useful in CONTACT tracing and in ascertaining when potentially contaminated food was ingested in cases of suspected food poisoning.

See also: LATENCY PERIOD

index case The first case identified in an outbreak of infectious disease.

See also: MARKER ORGANISM

EXHIBIT 3

a LANGE medical book

Basic & Clinical Biostatistics

fourth edition

Beth Dawson, PhD
Professor Emeritus
Biostatistics & Research
Department of Internal Medicine
Southern Illinois University
School of Medicine
Springfield, Illinois

Robert G. Trapp, MD
Medical Director
The Arthritis Center
Springfield, Illinois
Formerly
Assistant Professor and Chief of Rheumatology
Department of Internal Medicine
Southern Illinois University
School of Medicine
Springfield, Illinois

with the assistance of Amanda Greive, MPH

Lange Medical Books/McGraw-Hill
Medical Publishing Division

New York Chicago San Francisco Lisbon London Madrid
Mexico City Milan New Delhi San Juan
Seoul Singapore Sydney Toronto

[redacted]

The McGraw-Hill Companies

Basic & Clinical Biostatistics, Fourth Edition

1 2 3 4 5 6 7 8 9 0 DOC/DOC 0 9 8 7 6 5 4

Set ISBN: 0-07-141017-1

Book code: 0-07-141018-X

CD-ROM code: 0-07-141019-8

ISSN: 1045-5523

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

This book was set in Adobe Garamond by Pine Tree Composition, Inc.
The editors were Janet Foltin, Harriet Lebowitz, and Nicky Fernando.
The production supervisor was Catherine H. Saggese.
The illustration manager was Charissa Baker.
The cover designer was Mary McKeon.
The index was prepared by Jerry Ralya.
RR Donnelley was the printer and binder.

This book is printed on acid-free paper.

factorial design In ANOVA, a design in which each subject (or object) receives one level of each factor.

false-negative (FN) A test result that is negative in a person who has the disease.

false-positive (FP) A test result that is positive in a person who does not have the disease.

first quartile The 25th percentile.

Fisher's exact test An exact test for 2×2 contingency tables. It is used when the sample size is too small to use the chi-square test.

Fisher's *z* transformation A transformation of the correlation coefficient so that it is normally distributed.

focus groups A process in which a small group of people are interviewed about a topic or issue; often used to help generate questions for a survey, but may be used independently in qualitative research.

forward selection A model-building method in multiple regression that first enters into the regression equation the variable with the highest correlation, followed by the other variables one at a time that increase the multiple R by the greatest amount, until all statistically significant variables are included in the equation.

frequency The number of times a given value of an observation occurs. It is also called counts.

frequency distribution In a set of numerical observations, the list of values that occur along with the frequency of their occurrence. It may be set up as a frequency table or as a graph.

frequency polygon A line graph connecting the midpoints of the tops of the columns of a histogram. It is useful in comparing two frequency distributions.

frequency table A table showing the number or percentage of observations occurring at different values (or ranges of values) of a characteristic or variable.

functional status A measure of a person's ability to perform his or her daily activities, often called activities of daily living.

game theory A process of assigning subjective probabilities to outcomes from a decision.

gaussian distribution See *normal distribution.*

Gehan's test A statistical test of the equality of two survival curves.

Generalized estimating equations (GEE) A complex multivariate method used to analyze situations in which subjects are nested within groups when observations between subjects are not independent.

generalized Wilcoxon test See *Gehan's test.*

geometric mean (GM) The *n*th root of the product of n observations, symbolized GM or G. It is used with logarithms or skewed distributions.

gold standard In diagnostic testing, a procedure that always identifies the true condition—diseased or disease-free—of a patient.

Hawthorne effect A bias introduced into an observational study when the subjects know they are in a study, and it is this knowledge that affects their behavior.

hazard function The probability that a person dies in a certain time interval, given that the person has lived until the beginning of the interval. Its reciprocal is mean survival time.

hazard ratio Similar to the risk ratio, it is the ratio of risk of the outcome (such as death) occurring at any time in one group compared with another group.

hierarchical design A study design in which one or more of the treatments is nested within levels of another factor, such as patients within hospitals.

hierarchical regression A logical model-building method in multiple regression in which the investigators group variables according to their function and add them to the regression equation as a group or block.

histogram A graph of a frequency distribution of numerical observations.

historical cohort study A cohort study that uses existing records or historical data to determine the effect of a risk factor or exposure on a group of patients.

historical controls In clinical trials, previously collected observations on patients that are used as the control values against which the treatment is compared.

homogeneity The situation in which the standard deviation of the dependent (Y) variable is the same, regardless of the value of the independent (X) variable; an assumption in ANOVA and regression.

homoscedasticity See *homogeneity.*

Hosmer and Lemeshow's Goodness of Fit Test A multivariate test used to test the significance of the overall results from a logistic regression analysis.

hypothesis test An approach to statistical inference resulting in a decision to reject or not to reject the null hypothesis.

incidence A rate giving the proportion of people who develop a given disease or condition within a specified period of time.

independent events Events whose occurrence or outcome has no effect on the probability of the other.

independent groups or samples Samples for which the values in one group cannot be predicted from the values in the other group.

independent observations Observations determined at different times or by different individuals

EXHIBIT 4

The Encyclopaedic Companion to Medical Statistics

Edited by

Brian S. Everitt and Christopher R. Palmer

Hodder Arnold

A MEMBER OF THE HODDER HEADLINE GROUP

First published in Great Britain in 2005 by
Hodder Education, a member of the Hodder Headline Group,
338 Euston Road, London NW1 3BH

www.hoddereducation.com

Distributed in the United States of America by
Oxford University Press Inc.
198 Madison Avenue, New York, NY10016

Hodder Headline's policy is to use papers that are natural, renewable and recyclable products and made fromwood grown in sustainable forests. The logging and manufacturing processes are expected to conform to the environmental regulations of the country of origin.

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN-10: 0 340 80998 1
ISBN-13: 978 0 340 80998 3

1 2 3 4 5 6 7 8 9 10

Typeset in 9 on 10 Plantin by Phoenix Photosetting, Chatham, Kent
Printed and bound in Great Britain by Martins the Printers Ltd., Berwick upon Tweed

What do you think about this book? Or any other Hodder Education title? Please send your comments to the feedback section on www.hoddereducation.com

ICC Abbreviation for INTRACLUSTER CORRELATION COEFFICIENT.

ICER Abbreviation for incremental cost-effectiveness ratio. See COST-EFFECTIVENESS ANALYSIS

immune proportion The proportion of individuals who may not be subject to death, failure, relapse etc. in a sample of censored survival times. The presence of such individuals may be indicated by a relatively high number of individuals with large censored survival times. FINITE MIXTURE DISTRIBUTIONS can be used to investigate such data. Specifically, the population is assumed to consist of two components. The first, which is present in proportion, p, say, contains those individuals who are susceptible to some event of interest (death, relapse etc.) and have, say, an EXPONENTIAL DISTRIBUTION for the time to the occurrence of the event. These individuals are subject to right censoring. The remaining proportion $1 - p$ of the population is assumed to be immune to, or cured of, the disease and for these individuals the event never happens. Consequently, observations on their survival times are always censored at the limit of follow-up. An important aspect of such analysis is to consider whether or not an immune proportion does in fact exist in the population (see, for example, Maller and Zhou, 1995). *BSE*

[See also CURE MODELS]

Maller, R.A. and Zhou, S. 1995: Testing for the presence of immune or cured individuals in censored survival data. *Biometrics* 51, 181–201.

imputation See MULTIPLE IMPUTATION

incidence The incidence of a disease is the number of new cases of the disease occurring within a specified period of time in a defined population. A time period of 1 year is most commonly used, but any appropriate length of time can be substituted. It is generally presented as a rate. Thus:

$$\text{Incidence rate} = \frac{\text{Number of new cases of the disease in one year}}{\text{Number in the population at risk}}$$

This assumes that the size of the study population remains constant over the time period for which the rate is calculated. Small increases or decreases in population size over a year, for example, can be dealt with by using the mid-year population as the denominator for the incidence rate.

This results in a number between 0 and 1, but for ease of presentation it is often expressed as a rate per 1000, per 100,000 or per 1,000,000 depending on the disease rarity. As an example, the incidence rate of colorectal cancer in males aged 60–64 in Scotland was 200 per 100,000 in the year 2000 compared to 141 per 100,000 in 1990 (Scottish Health Statistics). Thus incidence rates can be used to measure risk and compare risks across time or between different populations.

This definition is rather simplistic because it ignores the fact that when new cases of the disease occur, the subject is no longer at risk and should ideally be removed from the denominator. It is also unsatisfactory for dealing with data from LONGITUDINAL STUDIES in which subjects may be followed up for varying lengths of time. For these studies the incidence rate can be defined as:

$$\text{Incidence rate} = \frac{\text{Number of new cases of the disease in the denned population}}{\text{Total length of time for which subjects have been followed up}}$$

The denominator gives the number of person-years of observation. Incidence rates defined in this way are often expressed as rates per 100 or per 1000 person-years of observation. (A more detailed discussion of incidence and incidence rates is given in Rothman and Greenland, 1998).

Care should be taken to distinguish between incidence and PREVALENCE. Although the definitions appear similar at first sight, they are used for different purposes and it is essential to distinguish between them correctly. *WHG*

Rothman, K.J. and Greenland, S. 1998: *Modern epidemiology*, 2nd edn. Philadelphia: Lippincott Wilkins and Williams. **Scottish Health Statistics:** www.isdscotland.org. **Woodward, M.** 1999: *Epidemiology: study design and data analysis*. Boca Raton: Chapman & Hall.

inclusion and exclusion criteria Criteria that operationalise choice of study group, a choice that lies at the heart of the design of, and inference from, CLINICAL TRIALS. 'Inclusion' criteria define the population of interest; 'exclusion' criteria remove people for whom the study treatment is contraindicated or unlikely to be effective. Collectively, inclusion criteria and exclusion criteria comprise the *entry criteria* or *eligibility criteria*. Biological plausibility, the internal validity of the study, the epidemiological basis for generalisability and statistical POWER all play parts in selecting entry criteria and in making recommendations from the results of the trial. The selection of those to be enrolled in a trial often reflects a deliberate attempt to select a study cohort homogeneous enough to allow a true treatment effect to become manifest, yet heterogeneous enough to permit reliable generalisation to a broader population. Clinical trials necessarily study people with more homogeneous characteristics than the patients to whom clinicians will apply the results.

Strict representativeness is relevant to the *generalisability* of clinical trials but not essential to *inference* from them. In randomised studies, the logical basis for drawing conclusions lies in the act of RANDOMISATION. The process of concluding that the effect seen in a clinical trial will apply to another population is informal and subjective (Cowan and Wittes, 1994).

Homogeneity of the study population differs from homogeneity of treatment effect. The former refers to a study group's sharing similar characteristics; the latter refers to an effect of treatment whose expected magnitude and direc-

EXHIBIT 5

ILLUSTRATED DICTIONARY *and* RESOURCE DIRECTORY *of*

ENVIRONMENTAL & OCCUPATIONAL HEALTH

Second Edition

Herman Koren

Co-published with the
National Environmental Health
Association

CRC PRESS

Boca Raton London New York Washington, D.C.

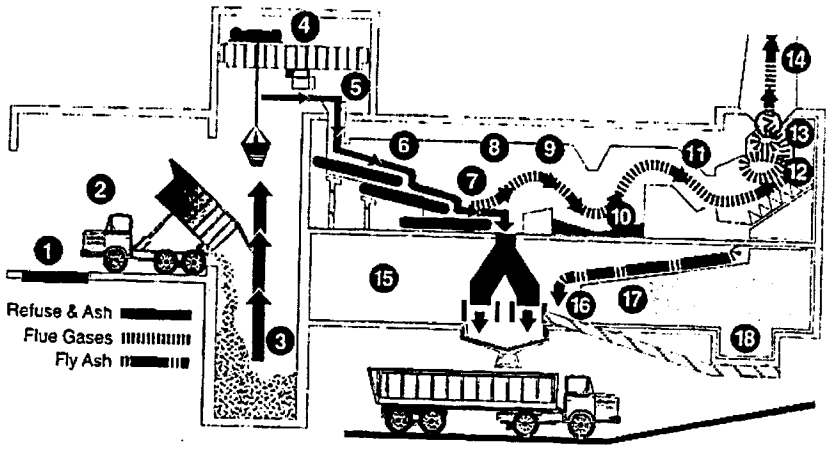
Library of Congress Cataloging-in-Publication Data

Koren, Herman.
Illustrated dictionary and resource directory of environmental and occupational health / Herman Koren. — 2nd ed.
p. cm.
Previous ed. published under the title: Illustrated dictionary of environmental health & occupational safety.
ISBN 1-56670-590-8 (alk. paper)
1. Environmental health—Dictionaries. 2. Industrial safety—Dictionaries. I. Koren, Herman. Illustrated dictionary of environmental health & occupational safety. II. Title.

RA566.K59 2004
616.9'8'003—dc22 2003065998

Visit the CRC Press Web site at www.crcpress.com

International Standard Book Number 1-56670-590-8
Library of Congress Card Number 2003065998
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper



1. Scales
2. Tipping Floor
3. Storage Bin (Pit)
4. Bridge Crane
5. Charging Hopper
6. Drying Grates
7. Burning Grates
8. Primary Combustion Chamber
9. Secondary Combustion Chamber
10. Spray Chamber
11. Breeching
12. Cyclone Dust Collector
13. Induced Draft Fan
14. Stack
15. Garage - Storage
16. Ash Conveyors
17. Forced Draft Fan
18. Fly Ash Settling Chamber

Basic Incinerator Design

a tungsten filament causes it to glow and produce a soft, warm light; much of the energy is lost as heat.

incapacitate — To take away the ability to perform normal activities or tasks.

incapacitated dose — The amount and concentration of chemical that causes an individual to be unable to perform normal activities or tasks.

incapacitating agent — A chemical that produces a temporary, disabling condition that lasts for hours or days after exposure has ceased.

incendiary device — Any mechanical, electrical, or chemical device used intentionally to initiate combustion or start a fire.

incendiary incident — An event in which an incendiary device is used as a terrorist weapon.

inch (in.) — A unit of length equal to 1/12 foot or 2.54 centimeters.

inchoate water right — An unperfected water right.

incidence — (*epidemiology*) The number of cases of disease, infection, or some other event having an onset during a prescribed period of time in relation to the unit of population in which they occur.

incidence rate — The rate at which new cases of a disease occur in a population at risk during a specified period of time; most useful in determining factors associated with the etiology of disease and in evaluating programs of prevention. Also known as incidence ratio.

incidence ratio — See incidence rate.

incident radiation — The quantity of radiant energy striking a surface per unit time and unit area.

incident report — The recording of any accident or deviation from policies or orders.

incidental parasite — An accidental parasite.

incineration — Controlled combustion of solid, liquid, or gaseous combustible wastes, which are ignited and burned to form carbon dioxide, water vapor, and other gaseous products; the solid residues contain little or no combustible material.

incinerator — An engineered piece of equipment used to burn waste substances; all of the factors of combustion, including temperature, retention time, turbulence, and combustion air, can be controlled.

incinerator residue — All solid material remaining after an incineration process is completed

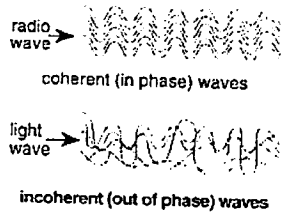
incipient — Describes a symptom or disease that is becoming apparent.

incision — A cut that is surgically produced using a sharp instrument to create an opening into an organ or space in the body.

incisive — Cutting into.

inclusion — A structure within another one.

incoherent waves — Waves for which the crests and troughs are not synchronized.



Incoherent Waves

EXHIBIT 6

GLOBAL BURDEN OF DISEASE AND INJURY SERIES
VOLUME II

GLOBAL HEALTH STATISTICS

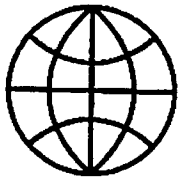
A Compendium of Incidence, Prevalence and Mortality Estimates for Over 200 Conditions

CHRISTOPHER J. L. MURRAY
HARVARD UNIVERSITY
BOSTON, MA, USA

ALAN D. LOPEZ
WORLD HEALTH ORGANIZATION
GENEVA, SWITZERLAND

WORLD HEALTH ORGANIZATION

HARVARD SCHOOL OF PUBLIC HEALTH



WORLD BANK

PUBLISHED BY THE HARVARD SCHOOL OF PUBLIC HEALTH ON BEHALF OF
THE WORLD HEALTH ORGANIZATION AND THE WORLD BANK
DISTRIBUTED BY HARVARD UNIVERSITY PRESS

Library of Congress Cataloging-in-Publication (CIP) Data

Murray, Christopher J.L.

Global health statistics : a compendium of incidence, prevalence, and mortality estimates for over 200 conditions / Christopher J.L. Murray, Alan D. Lopez.

p. cm. -- (Global burden of disease and injury series : 2)

"Harvard School of Public Health."

Includes bibliographical references and index.

Introd. also in Spanish and French.

ISBN 0-674-35449-4

1. Medical statistics. I. Lopez, Alan D. II. World Health Organization. III. World Bank. IV. Harvard School of Public Health. V. Title VI. Series.

[DNLM: 1. Epidemiology--tables. 2. Public Health--statistics. 3. Health Status Indicators--tables. WA 16 M981g 1996]

RA407. M87 1996

614.4'2--dc20

DNLM/DLC

for Library of Congress 96-26652

CIP

Printed in the United States of America

The authors alone are responsible for the views expressed in this publication.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Bank and the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

For Brian Abel-Smith, Richard Peto, Sam Preston, Lado Ruzicka and Edward O. Wilson who guided and encouraged us in our careers; and for Agnes and Lene, our infinitely patient and supporting wives.

Table IV (continued)

GBD Classification Code		Cause group, disease, injury, or sequela	Data presented in this volume (table number)
IIIB2-32		Burns < 20% – short term	
IIIB2-33		Burns < 20% – long term	
IIIB2-34		Burns > 20% and < 60% – short term	
IIIB2-35		Burns > 20% and < 60% – long term	
IIIB2-36		Burns > 60% – short term	
IIIB2-37		Burns > 60% – long term	
IIIB2-38		Injured nerves	243
IIIB2-39		Poisoning	
IIIB2-40		Residual	
IIIB3	War		
IIIB3-1		Episodes	244
IIIB3-2		Fractured skull – short term	
IIIB3-3		Fractured skull – long term	
IIIB3-4		Fractured face bones	
IIIB3-5		Fractured vertebral column	
IIIB3-6		Injured spinal cord	
IIIB3-7		Fractured rib or sternum	
IIIB3-8		Fractured pelvis	
IIIB3-9		Fractured clavicle, scapula, or humerus	
IIIB3-10		Fractured radius or ulna	
IIIB3-11		Fractured hand bones	
IIIB3-12		Fractured femur – short term	
IIIB3-13		Fractured femur – long term	
IIIB3-14		Fractured patella, tibia, or fibula	
IIIB3-15		Fractured ankle	
IIIB3-16		Fractured foot bones	
IIIB3-17		Other dislocation	
IIIB3-18		Dislocated shoulder, elbow, or hip	
IIIB3-19		Sprains	
IIIB3-20		Intracranial injury – short term	
IIIB3-21		Intracranial injury – long term	245
IIIB3-22		Internal injuries	
IIIB3-23		Open wound	
IIIB3-24		Injury to eyes	
IIIB3-25		Amputated thumb	
IIIB3-26		Amputated finger	
IIIB3-27		Amputated arm	246
IIIB3-28		Amputated toe	
IIIB3-29		Amputated foot	247
IIIB3-30		Amputated leg	
IIIB3-31		Crushing	
IIIB3-32		Burns < 20% – short term	
IIIB3-33		Burns < 20% – long term	248
IIIB3-34		Burns > 20% and < 60% – short term	
IIIB3-35		Burns > 20% and < 60% – long term	
IIIB3-36		Burns > 60% – short term	
IIIB3-37		Burns > 60% – long term	
IIIB3-38		Injured nerves	249
IIIB3-39		Poisoning	
IIIB3-40		Residual	

occurs early or later in life, how long, on average, does the condition persist and how many people die from the condition in different population subgroups.

The format of the tables is as follows. At the top of the page, the abbreviated disease or injury short title is provided. Directly beneath the short disease or injury name is the name of the sequela. Three different terms are used repetitively to describe some sequelae: episodes, cases, and symptomatic cases. For diarrhoeal diseases, only one sequela is provided, namely episodes of diarrhoea itself. For consistency, all outcomes related to a disease, including the primary manifestation of the disease or injury, are called sequelae. When the term episodes is used, it indicates that we are providing estimates of incidence and prevalence of episodes of the disease or injury. For some chronic conditions, we provide estimates of the incidence or prevalence of individuals with the condition such as diabetes—this is indicated by using the term cases. Finally, for other chronic conditions, such as COPD or cirrhosis, we have given estimates of the incidence or prevalence of individuals with symptoms of the disease, labelled as symptomatic cases.

The following descriptions and definitions apply to all tables.

Reference year: all estimates refer to calendar year 1990, the base year for the Global Burden of Disease Study. The single exception is the projection of mortality which is shown for the year 2000.

Demographic variables: estimates are presented separately for males and females in view of their different risks of incurring disease and injury. Estimates are shown first for males in the top half of each table, and then for females in the bottom half of the table. Age is perhaps the most important variable in describing disease and injury patterns, since virtually all conditions reported in this book are strongly age-dependent. Estimates are presented for five broad age groups which roughly describe the phases of the life cycle during which disease and injury patterns are likely to be similar. Estimates are also presented for all ages combined, without any attempt at age-standardization. At the bottom of each table, estimates are provided for the total population of the region, including all age groups and for males and females combined.

Incidence: this indicator measures the occurrence of new cases of disease or injury in 1990. The estimated *number* of new cases (in thousands) is shown, along with the estimated incidence rate in the region, expressed as the number of new cases per 100 000 population per year in the respective age-sex group.

Prevalence: in addition to estimating the number of new cases, it is important to be able to estimate the amount of disease or injury which was actually present in each region in 1990, either due to new cases (incidence) in 1990, or from previous years. The estimated number (in thousands) of prevalent cases of disease or injury in 1990 is shown in the

CERTIFICATE OF SERVICE

I hereby certify that on this 15th day of May, 2007, I electronically filed the foregoing document, **REDACTED VERSION OF DECLARATION OF BERTRAM A. SPILKER, M.D., Ph.D., F.C.P., F.F.P.M. IN SUPPORT OF DEFENDANT'S MARKMAN BRIEF,** with the Clerk of the Court using CM/ECF which sent notification of such filing to the following:

Jack B. Blumenfeld
Karen Jacobs Louden
Morris Nichols Arsht & Tunnell
1201 N. Market Street
Wilmington, DE 19801

Additionally, I hereby certify that the foregoing document was served as indicated below:

VIA EMAIL

Jack B. Blumenfeld
Karen Jacobs Louden
Morris Nichols Arsht & Tunnell
1201 N. Market Street
Wilmington, DE 19801
jblumenfeld@mnat.com
klouden@mnat.com

VIA EMAIL

Basil J. Lewris
Linda A. Wadler
Finnegan Henderson Farabow
Garrett & Dunner
901 New York Avenue, NW
Washington, DE 20001
Bill.Lewris@finnegan.com
Linda.Wadler@finnegan.com

/s/ Mary B. Matterer
Mary B. Matterer (I.D. No. 2696)
Morris James LLP
500 Delaware Avenue, 15th Floor
Wilmington, DE 19801
(302) 888-6800
mmatterer@morrisjames.com

Attorneys for IMPAX LABORATORIES, INC.